CYCLOSPORIN FORMULATIONS OF MONO OR DIGLYCERIDE FATTY ACID

This application is a continuation of application Ser. No. 07/303,646, filed Jan. 27, 1989, now abandoned.

BACKGROUND TO THE INVENTION

The present invention relates to a novel pharmaceutical composition wherein at least one cyclosporin, which is the active ingredient, is accompanied by a solubilising agent which is a mono- or di- glyceride of an intermediate molecular weight fatty acid (i.e. a fatty acid having from 6 to 10 carbon atoms).

The cyclosporins are a homologous group of biologically active oligopeptides, which are metabolites produced by certain fungi imperfecti. Cyclosporin A is the best known member of this group, but cyclosporins B to I have also so far been identified, and the commercially available product may contain a mixture of several individual cyclosporins. They all share a cyclic peptide structure consisting of 11 amino acid residues with a total molecular weight of about 1,200, but with different substituents or configuration of some of the amino acids [Merck Index, 2748, 10th Ed.; Helv. Chim. Acta 60, 1568–1578 (1977); Helv, Chim. Acta 65, 1655–1677 (1982)].

For convenience, the term "cyclosporin" (in the singular and without further qualification) will be used hereinafter to designate the cyclosporin component of the composition of the present invention. However, it should be understood that, as used with reference to the invention, this term is intended to include any individual member of the cyclosporin group, as well as mixtures of two or more such individual cyclosporins whether of two or more such individual cyclosporins whether in the form of commercially available mixtures or otherwise.

Cyclosporin has immunosuppressive, antifungal and antiphlogistic activities, but has so far been primarily used therapeutically for its immunosuppressive activity. In its therapeutic use as an immunosuppressive, it is currently used either orally or by injection. However, since the solubility of cyclosporin in water is extremely low (e.g 20 μg/ml to 30 μg/ml for cyclosporin A), both types of formulation are prepared as an oily solution containing ethanol. Even so, the bioavailability of its oral preparations is extremely low, generally below 30% [K. Takada et al. Drug Delivery System 1, No. 1, 1–7 (1986)]. This is believed to be due to the separation of cyclosporin as a solid immediately after it comes into contact with water, e.g. in the mouth or in the gut. Injectable preparations of cyclosporin formed as an oily solution containing ethanol have first to be diluted with physiological saline before intravenous administration. In the case of intravenous administration, however, it is clearly not merely undesirable but highly dangerous for cyclosporin to separate out on contact with water. Accordingly, a surface active agent, such as a polyoxyethylated castor oil, is added as a solubilizer to injectable preparations in order to prevent the cyclosporin from separating out. However, the addition of surface active agents, such as polyoxyethylated castor oil, to injectable preparations can give rise to safety problems.

Cyclosporin is effective in the treatment of the ocular symptoms of Behcet's Syndrome. When it is administered orally for the treatment of these symptoms and relies upon systemic circulation to reach the eyes, the side effects of the drug may cause various adverse reactions, such as hypertrichosis or renal dysfunction. However, when oily preparations containing cyclosporin are applied directly to the eyes, irritation or a clouded visual field may frequently result. Hence, cyclosporin is, in reality, of little practical use in the treatment of the ocular symptoms of Behcet's Syndrome, for which it would otherwise be very well suited. Moreover, if it were possible to prepare a formulation suitable for topical application to the eyes, it would be expected to have various other uses in addition to the treatment of the ocular symptoms of Behcet's Syndrome. For example, from its pharmacological mode of action, it is thought that it could be useful during keratoplasty as well as in the treatment of herpetic keratitis and spring catarrh.

One way of overcoming the problem of inadequate water solubility would be to dissolve sufficient cyclosporin in an aqueous solvent system so as to reach an effective concentration for treatment. Such a solvent system should not contain any additive, such as a surface active agent, which could give rise to safety problems. If this could be achieved, the cyclosporin would already be in an aqueous solution and its contact with bodily fluids would merely constitute dilution, so that it would not immediately separate out when contacted with the water of such fluids. However, so far it has been very difficult to make any such preparation because cyclosporin has an extremely low solubility in water and has a cyclic structure with a molecular weight significantly greater than 1,000, with the result that insufficient can be dissolved to be effective for the desired treatment. Table 1 shows the solubility of cyclosporin A in various kinds of solvents, from which it can be seen that the solubility pattern seems quite unique.

TABLE 1

Solvent	Solubility parameters δd	δp	δh	Solubility of cyclosporin A [mg/ml]
Methanol	7.4	6.0	10.9	>1000
Ethanol	7.7	4.3	9.5	>1000
Acetonitrile	7.5	8.8	3.0	>1000
Ethyl acetate	7.4	2.6	4.5	>1000
Benzene	8.9	0.5	1.0	400
Tetrahydrofuran	8.2	2.8	3.9	400
Acetone	7.6	5.1	3.4	100
Propylene glycol	8.2	4.6	11.4	100
Isopropanol	7.7	3.0	8.0	50
Cyclohexane	8.2	0.0	0.0	20
Hexane	7.2	0.0	0.0	<10
Water	6.0	15.3	16.7	<1

In the above Table, δd, δp and δh are measures of dispersion force, polarity and hydrogen bonding, respectively.

In view of these solubility properties, it has, in the past, been considered not merely difficult but practically impossible to design reasonably a pharmaceutical composition containing cyclosporin dissolved in an aqueous medium.

Although the cyclosporins have demonstrated some solubility in oily preparations containing higher fatty acid glycerides, such as olive oil, peanut oil and/or castor oil, these frequently produce an unpleasant sensation when applied to the eye because of stimulation or the viscousness which is characteristic of these oils.

We have previously proposed in USSN 201 579, filed 1st of June, 1988, to solubilise cyclosporin by using it in admixture with at least one α-cyclodextrin and/or de-